PATENT
ATTORNEY DOCKET NO. 044137-5025-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Alan SOLOMON *et al.*

Application No.: 09/316,387

Filed: May 21, 1999

For: METHODS FOR AMYLOID REMOVAL USING ANTI-AMYLOID ANTIBODIES

Group Art Unit: 1647

Examiner: S. Turner

#41
1647
7/15/03

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, the undersigned, Anja Leona Biere, do hereby declare that:

1. I am a German citizen, residing at Thousand Oaks, California.

2. I have been awarded a doctorate in Molecular Biology from the Max-Planck-Institute/Free University in Berlin, Germany.

3. I have been employed by Amgen since 1997 and I am presently a Research Scientist at Amgen. During my employment at Amgen, I have been engaged in research and development in the area of amyloidosis including Alzheimer's disease.

4. I have reviewed the Final Office Action, and I have reviewed the references of Walker *et al.*, Konig *et al.*, Becker *et al.*, and Benjamini, cited by the Examiner in a rejection of

claims 23-27, 29-35, and 37-45. I believe the claims are not obvious over the cited references for at least the following reasons:

A. The focus of amyloidosis research and the method of treatment employed by physicians at the time of Applicants' invention make the claimed invention unobvious.

At the time of Applicants' invention, most of the research in amyloidosis was targeted at inhibiting precursor production to reduce amyloid aggregation (Kisilevsky, R, *Drugs & Aging*, 1996; 8 (2):75-83). Unlike amyloid deposits which are highly insoluble, resistant to proteases, and irreversible (Kuo *et al.*, *The Journal of Biological Chemistry*, 1996, 271(8):4077-4081), the precursor proteins are soluble and easily degraded by proteases. The scientists in the field of amyloidosis at that time focused on inhibiting the production or enhancing the clearance of the monomeric, soluble precursor protein instead of the aggregated fibrils. Thus, since amyloids are extremely stable entities, therapeutic clearance of amyloid deposits was never considered as an option.

Researchers at the time of Applicants' invention also attempted to inhibit amyloid formation through the use of small molecule or peptide aggregation inhibitors, which stabilized certain conformations of soluble precursor molecules to prevent aggregation (Tjernberg *et al.*, *Journal of Biological Chemistry*, 1996, 271(15):8545-8548).

At the time of Applicants' invention, therapy for peripheral amyloidosis was focused on the affected organ. For example, physicians treated secondary and hereditary amyloidoses by surgically removing the amyloid deposits. Alternatively, physicians treated primary amyloidosis with conventional doses of chemotherapy or high doses in combination with autologous stem cell transplantation (Falk *et al.*, *The New England Journal of Medicine*, 1997, 337(13):898-908).

B. The successful use of antibodies to treat amyloidosis was unexpected.

Prior to Applicants' invention, antibodies against amyloids had only been used as research tools and for diagnostic purposes. Antibodies were not used to treat patients suffering from amyloidosis.

Moreover, at the time of Applicant's invention, the general belief was that amyloid deposits were not considered foreign materials by the human body. Amyloid deposits in humans do not induce a humoral (antibody-based) immune response. Thus, at the time of Applicants' invention, neither active nor passive immunization was considered by the amyloidosis research community as an efficacious method of treating amyloidosis. Even after the successful clearance of amyloid deposits using Aβ peptide vaccines subsequent to Applicants' discovery (Schenk *et al.*, *Nature*, 1999, 400:173-177), it was not known whether the resulting effect was due to antibody production because vaccines induce a variety of immune responses. The production of antibodies is only one aspect of an immune response (Lee, V., *Proceedings of National Academy of Sciences*, 2001, 98(16):8931-8932). In fact, T-cell activation was thought to be the natural line defense against the accumulation of Aβ (Grubeck-Loebenstein, 2000, *TINS*, 23(3):114). Accordingly, it was not obvious at the time of Applicants' invention that passive immunization of a patient with antibodies would be effective in treating amyloidosis.

C. The effectiveness of antibodies as diagnostic tools for detecting amyloid deposits *in vitro* is not predictive of the effectiveness of the antibodies for inhibiting or modulating the formation of amyloid deposits in a patient or for removing amyloid deposition from a patient.

The cited references Walker *et al.* and Konig *et al.* disclose antibodies that are asserted to be useful for detecting amyloid deposits. Although Becker *et al.* may provide a general suggestion of the use of antibodies in the treatment of amyloidosis, notably, they fail to provide any method for obtaining such antibodies against amyloid fibrils. Benjamini merely provides a definition for opsonization. Thus, none of these cited references, even in combination, provide antibodies or methods for inhibiting or modulating the formation of amyloid deposits or the removal of amyloid deposits from a patient.

The binding of antibodies to inhibit or modulate the formation of amyloid deposits in a patient or the removal of amyloid deposits from a patient is a more complex process than the binding of an antibody to an amyloid deposit for diagnostic detection. To detect an amyloid

deposit, the antibody just needs to bind somewhere on a component of the amyloid deposit. To inhibit or modulate the formation of amyloid deposit in a patient or to remove an amyloid deposit from a patient, a specific antibody requires additional properties beyond mere binding. These properties may include (i) binding to specific epitopes involved in amyloid fibril formation; and (ii) inducing effector functions. Induction of these functions require an antibody of a specific class (e.g. IgG, IgM, IgE, IgA, IgD) and isotype (*e.g.* human IgG γ1, γ2, γ3, γ4) together with additional components of the immune system. In addition, these functions are highly dependent upon a number of factors including antibody flexibility, carbohydrate structure and antigen density.

Accordingly, it is not predictable that the antibodies of Walker *et al.* and Konig *et al.* or the antibody generated by following the teachings of Becker *et al.* would have been effective in inhibiting or modulating the formation of amyloid deposits in a patient or removing amyloid deposits from a patient. Both Walker *et al.* and Konig *et al.* show that their antibodies were useful as research tools for detecting amyloid deposits. However, these references do not provide evidence that the antibodies can be used to treat patients by inhibiting or modulating the formation of amyloid fibril or by removing amyloid deposits. Benjamini does not provide the missing elements to cure the deficiency of Walker *et al.*, Konig *et al.* and Becker *et al.* Thus, the cited references do not render the claimed invention obvious.

D. Conclusion

For the reasons discussed above, Applicants' invention is not obvious over the cited references. Applicants unexpectedly discovered that antibodies are effective in treating amyloidosis in a patient. For the reasons discussed above, it was not obvious to use antibodies to treat patients at the time of Applicants' invention. Although the cited references confirm that, at the time of Applicants' invention, antibodies generated against amyloid were useful in detecting amyloid deposits ex vivo, the references fail to show that such antibodies can be used to inhibit or modulate the formation of amyloid deposits in a patient or to remove amyloid deposits from a patient.

5. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10/23/2002 By: Alejandra Brea